

# Automatic Activation of the Medial Temporal Lobe During Encoding: Lateralized Influences of Meaning and Novelty

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**ABSTRACT:** In contrast to early failures, recent functional brain imaging studies have shown that medial temporal lobe (MTL) structures are active during performance of a variety of tasks. These studies have revealed three properties of the MTL that are consistent with its critical role in establishing new declarative memories. First, the MTL is automatically engaged whenever an event is experienced, with the side of activation (left, right) dependent on the nature of the material presented (verbal, nonverbal). Second, the strength or amount of activity depends on how well the material is encoded. Deep encoding will produce more MTL activity than shallow encoding. Depth of encoding-related increases in activity are more commonly seen on the left, because deep encoding is nearly always synonymous with encoding for meaning, and, therefore, depends on left-lateralized language mechanisms. Third, the amount of MTL activity depends on novelty. Unfamiliar events and contexts will produce more MTL activity than familiar events and contexts. Novelty-related increases are more commonly seen on the right, perhaps reflecting the greater role of the right hemisphere in maintaining tonic attention and arousal. These findings suggest a hemispheric division of labor involving encoding for meaning (left) and novelty detection (right), both of which lead to better remembering. *Hippocampus* 1999;9:62–70. Published 1999 Wiley-Liss, Inc.<sup>†</sup>

**KEY WORDS:** memory; hippocampus; medial temporal lobe; positron emission tomography (PET)

## INTRODUCTION

A basic assumption of neuropsychological, computational, and neurophysiological models of the medial temporal lobe (MTL) memory system (hippocampus and entorhinal, perirhinal, and parahippocampal cortices) is that this region of the brain is active when events are experienced. Parahippocampal and perirhinal cortex receive information from all unimodal and polymodal cortical processing areas, and this information, in turn, is transmitted to entorhinal cortex, and then to the hippocampus (see Suzuki, 1996, for review). When these structures are damaged, the acquisition of facts and events is severely impaired, with dire consequences for everyday life. Amnesic patients fail to retain information that is normally acquired incidentally, without specific effort or intention to learn and remember. Given the critical role assigned to this brain region in

creating declarative memories, one would expect that activity in this region would be among the most common findings in functional brain imaging studies.

To clarify why this should be so, consider the following scenario. A group of patients with global amnesia resulting from bilateral MTL damage and a group of normal individuals participate in a brain imaging study. The subjects are required to read words and name objects. What would we predict from such a study? First, behaviorally, the patients and the normal subjects would be expected to have equivalent levels of performance. By definition, the amnesic patients would read and name as well as the normal individuals. Now imagine that we question the subjects at some later time about the experiment. Even though they were not explicitly asked to learn and remember, normal subjects would be able to describe their experience. They would provide information about context (when and where events occurred) and content (what they were asked to do, and the names of at least some of the objects and words that were presented). For the amnesic subjects, we would expect a very different pattern of behavior. Not only would they provide little detail about the experience, they likely would not remember that they had taken part in a brain imaging experiment at all. We would, of course, ascribe this dramatic difference in behavior to the fact that the MTL was damaged in the patients and not in the normal controls. But if this difference is due to the MTL, then wouldn't that require that the MTL was active in the normal subjects during the experiment? And, if so, then why isn't MTL activation a common finding in functional brain imaging studies of normal individuals?

One possibility is suggested by the scenario described above. Normal subjects can remember the imaging experiment, and this memory would likely include some information about the various experimental conditions, including those that the investigator considered baseline conditions. If finding process-specific activations depends on comparing one condition to another (subtraction), then activity in the MTL may not be found because it was active during both conditions, and therefore subtracted away when the scans were contrasted.

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This idea, which was first suggested by Fletcher and colleagues (1995) to account for the lack of MTL activation in their study as well as others that had appeared in the literature, seems a very reasonable, and highly likely, possibility. The MTL must be automatically engaged whenever we attend to an event. Its participation at the time of encoding is obligatory (although certainly not sufficient) for remembering. Again, if it was not, then how do we remember events that we never set out to learn and remember? And, why would incidental learning fail to occur when this region is damaged? With this framework in mind, the question then becomes: What conditions are necessary to demonstrate automatic activation of the MTL using functional brain imaging?

One approach to this problem, suggested by Fletcher et al. (1995), is to abandon the subtraction method in favor of a correlational approach that relates changes in regional brain activity to performance. An alternative approach would be to try to find an appropriate baseline for comparison purposes. This is the approach we took, in the context of a design that took advantage of two well-established facts about episodic memory (Martin et al., 1997).

The first fact comes from studies of patients with focal brain lesions. Left MTL damage interferes with learning and remembering verbal material to a greater extent than right MTL lesions (e.g., Milner, 1972), whereas right MTL damage disrupts memory for nonverbal material to a greater extent than left MTL lesions (e.g., Kimura, 1963). Demonstrating MTL hemispheric differences as a function of stimulus type would bolster claims that the activity revealed by functional brain imaging is related to encoding operations. To this end, we included material that lends itself to verbal encoding (words, namable objects) and material that does not (nonsense objects).

The second fact is that memory is better for items that are processed deeply (semantically encoded) than for items that are processed shallowly (perceptually encoded) (e.g., Craik and Lockhart, 1972). Demonstrating that the strength of MTL activity varies as a function of whether the material is semantically encoded (and, therefore, better remembered) would also serve to bolster claims that the activity revealed by functional brain imaging is related to encoding operations. Therefore, we included material that automatically engages semantic processing (real words and objects; Bajo, 1988) and material that does not (nonsense words and objects). Material that naturally lends itself to semantic processing should be better remembered, and should be associated with enhanced MTL activity, relative to material without pre-existing semantic representations.<sup>1</sup>

It is noteworthy that this approach to studying the effects of encoding operations differs markedly from the paradigm commonly employed in memory experiments. Invariably, the to-be-studied material is held constant (e.g., meaningful words), and the nature of the encoding operation is varied by requiring subjects to attend to different aspects of the stimulus. Deep encoding is elicited by a semantic orienting task (e.g., judging whether the word represents a living thing) and shallow encoding is elicited by a perceptual orienting task (e.g., judging whether the word contains a particular letter), thereby ensuring that the effect on memory is due to the encoding operation, rather than to differences in the material presented. In contrast, the approach taken here was to vary the nature of the material (real words, nonsense words), while keeping the task relatively constant (reading). This approach was taken for two reasons. First, we were interested in demonstrating automatic engagement of the MTL under relatively naturalistic processing modes (reading, naming, viewing). Demonstrating modulation of MTL under typical levels of processing conditions would leave open the question of whether the MTL is automatically engaged simply by attending to a stimulus. Second, previous attempts to modulate MTL activity as a function of encoding operations had been unsuccessful. For example, Kapur and colleagues (1994) presented subjects with concrete nouns. During one PET scan they instructed the subjects to decide whether the words referred to a living thing, and during another scan to decide if the words contained the letter "a." Deep encoding produced greater activity in left prefrontal cortex compared to shallow encoding. However, no change in MTL activity was detected. One explanation for this failure is that it may be impossible to completely inhibit semantic encoding of familiar words, even when subjects are instructed to attend to surface features (e.g., Price et al., 1996b). Therefore, the regions associated with semantic encoding may have been active in both conditions, albeit more strongly for deep than shallow encoding, but this difference may have been too subtle to be detected by PET.

The final issue concerned the choice of a baseline task. If the side and amount of MTL activity varies with the type of material presented, then perhaps a baseline task that captures the subject's attention, yet contains no specific stimulus information, might produce minimal MTL activity and thus provide a background against which activity in this region could be detected. To accomplish this goal, we presented visual noise stimuli (similar to static on a TV), with different examples shown briefly (180 msec), once every 2 seconds. This baseline task was compared with scans during which subjects silently encoded different types of material presented for the same duration, and at the same rate, as the visual noise. During these encoding scans, subjects were instructed to attend to nonsense objects, silently name real objects, silently read pronounceable nonsense words, and silently read real words. There were two scans for each of these conditions, but with different, not previously seen, items during each scan. Subjects were not instructed to learn the material nor was memory tested at any time during the experiment.

<sup>1</sup>It is likely that subjects engage in some semantic processing of nonsense words and objects. After all, even categorizing items as meaningless, rather than meaningful, is a semantic decision. However, whereas real words and real objects have well established meanings that are shared by members of a culture, nonsense words and objects do not. Semantic interpretations of nonsense words and objects will likely be inconsistently applied and idiosyncratic. In this sense, comparison of real objects and words to nonsense objects and words may constitute a comparison of deep to shallow semantic processing.

## AUTOMATIC ACTIVATION OF THE MTL DURING ENCODING: MATERIAL-SPECIFIC HEMISPHERIC ASYMMETRIES

The first finding that emerged from this study was that the MTL was automatically engaged by these tasks. Relative to viewing visual noise, viewing nonsense objects, naming real objects, and reading nonsense words and real words, were all associated with MTL activity. Moreover, the activations were lateralized according to stimulus type. Word reading (meaningful and meaningless) produced left MTL activity, viewing nonsense objects produced strong right-sided and weak left -sided MTL activity, and naming objects was associated with robust, bilateral and symmetrical activation of the MTL.

These findings were as one would predict based on studies of patients with lateralized cerebral lesions that include the MTL. For example, left temporal lobectomy patients have shown impaired memory for meaningful words (e.g., Milner, 1972) and nonmeaningful syllables (Milner and Kimura, 1964). In contrast, right temporal lobectomy patients perform worse than left lesioned patients on memory for items that are not easily encoded verbally, including nonsense designs (Kimura, 1963). Finally, both left and right temporal lobectomy patients have poor recall of the names of previously presented objects (Smith and Milner, 1981).

Review of the functional brain imaging literature reveals that similar findings have been reported in studies of word and object processing in which subjects were not explicitly instructed to learn and remember (i.e., incidental encoding into memory). For example, several studies have reported an association between left MTL activity and processing real words and pronounceable, but meaningless letter strings. Price and colleagues reported left MTL activity for reading real words relative to performing a feature detection task on false font stimuli, and for making word/nonsense word judgments versus the false font feature detection task (Price et al., 1994). These investigators also found left MTL activation when subjects performed a letter-feature detection task on nonsense words relative to performing the same task on consonant letter strings (Price et al., 1996b). Similarly, Bookheimer et al. (1995), reported left MTL activity for reading real words relative to viewing meaningless, random line drawings. In contrast, other studies have reported activation of the right MTL for viewing nonsense objects relative to viewing visual noise patterns (Martin et al., 1996) and relative to a visual fixation task (Zelkowitz et al., 1998). Finally, bilateral activation of the MTL was found when subjects made living/nonliving judgments of objects relative to judging the spatial orientation of single letters (Sergent et al., 1992; Bookheimer et al., 1995) reported MTL activation for silently naming objects relative to viewing meaningless, random line drawings, but this activity was limited to the left MTL. A similar finding was reported by Martin et al., 1997.

These examples of lateralized MTL activity associated with incidental learning are consistent with other functional brain imaging studies in which subjects were explicitly instructed to

learn and remember (i.e., intentional encoding into memory). Activity lateralized to the left MTL has been found for encoding meaningful words (Wagner et al., 1998; S. Kapur et al., 1996; Dolan and Fletcher, 1997; Nyberg et al., 1996), and bilateral MTL activity has been found for encoding of meaningful objects and scenes (Kelley et al., 1998; Stern et al., 1996; Gabrieli et al., 1997; Brewer et al., 1998). Functional brain imaging studies of memory for nonsense objects under intentional learning instructions have not been reported. However, studies of intentional learning of unfamiliar (and therefore difficult to verbally encode) human faces (Haxby et al., 1996; Kapur, et al., 1995; Kelley et al., 1998), and spatial locations (Maguire et al., 1998) have reported MTL activity that was stronger on the right, than the left.

Thus, there are now a number of findings of appropriately lateralized MTL activity in normal subjects, and these findings have been observed under both incidental and intentional encoding conditions. The difference between incidental and intentional encoding was directly evaluated by Kelley et al. (1998) using functional magnetic resonance imaging (fMRI). Although the activations associated with incidental encoding failed to reach statistically significant levels, inspection of their data suggests that the difference between incidental and intentional encoding was quantitative, not qualitative. Incidental encoding produced the same material-specific hemispheric pattern of MTL activity that was produced by intentional encoding instructions. The encoding-related activations, however, were substantially stronger when subjects were explicitly instructed to learn the material for a subsequent memory test, relative to when they were told to simply view the stimuli. This passive viewing instructional set may also account for the difference between our more robust findings and those reported by Kelley and colleagues (1998). We explicitly instructed our subjects to name and read the words, name the real objects, and carefully attend to each nonsense object rather than to simply view the material. Incidental encoding and intentional encoding appear to produce the same pattern of MTL activity based on the type of material presented for processing. Intentional encoding may simply serve to boost attention and other cognitive processes that subjects would normally use for processing different types of material (words, objects). Thus, for MTL activity, the difference between these instructional sets appears to be one of degree, not kind.

Based on these and other findings, there is now ample evidence in the functional brain imaging literature that the MTL is automatically engaged when we attend to an event (see Schacter and Wagner, 1998, this issue, for a more complete list of encoding-related MTL activations). Moreover, the lateralization of these activations is consistent with findings from patients with unilateral damage to the MTL and surrounding cortex. Thus, despite early fears of contradictory, or divergent findings, there appears to be convergence between the human lesion and functional brain imaging data about the role of MTL in encoding operations. This conclusion, however, must be considered within the context of a large number of studies of incidental and intentional encoding that have failed to find MTL activations. Possible reasons for these failures will be discussed at the end of this commentary.



## SEMANTIC PROCESSING AND THE LEFT MTL

The second finding that emerged from our study was that the strength of left MTL activity varied as a function of meaning, regardless of physical format. All types of material produced activation of the left MTL, but this activity was substantially greater for real objects compared to nonsense objects, and real words compared to nonsense words. In contrast, the right MTL responded strongly to objects, regardless of their inherent meaning (for details see Martin et al., 1997).

To illustrate this point, a direct comparison of the PET data collected when subjects processed meaningful material (objects and words), relative to when they processed meaningless material (objects and words), is presented in Figure 1. Compared to viewing nonsense objects and reading nonsense words, encoding meaningful material (naming objects, reading words) produced greater activation of the left MTL, as well as the left inferior temporal cortex (BA 37) and left inferior prefrontal cortex (BA 45). Importantly, and in contrast to the difference between intentional and incidental encoding, the difference between encoding meaningful and meaningless material was not due to increased attentional demands. In fact, reading nonsense words typically takes longer than reading real words (Wiggs and Martin, 1994). Reading real and reading nonsense words produced activity in the same location in the left MTL, but this activity was greater for the easier encoding task (reading real words) than for the more difficult encoding task (reading nonsense words).

As expected, a separate behavioral study confirmed that subjects had better recognition memory for incidentally encoded meaningful material than for meaningless items (Martin et al., 1997). Thus, taken together, these results suggest that semantic encoding (and better explicit memory) is associated with activation of a network of left hemisphere sites that includes the inferior prefrontal cortex, inferior temporal cortex, and the MTL.

Increased left MTL activity for semantic, relative to shallower, encoding was first reported by Kapur and colleagues (1996), and more recently by Wagner et al. (1998). In addition, using elegant, event-related designs with MRI, Wagner and colleagues (1998), and Brewer and colleagues (1998), have shown that the likelihood that a specific item will be remembered is directly related to the strength of MTL activity recorded when that item was initially encoded (see Fernandez et al., 1998, for a similar finding using a correlational analysis).

Moreover, and consistent with the findings presented above, depth of encoding-related increases in MTL activity do not occur in isolation. Rather, enhanced MTL activity occurs in unison with increases in prefrontal cortex and the posterior temporal lobe. Left prefrontal cortex has been shown to be more active during semantic encoding, relative to shallower encoding, under both incidental encoding (Kapur et al., 1994, 1996; Domb et al., 1995; Wagner et al., 1998, Experiment 1) and intentional encoding conditions (Kapur et al., 1996; Decety et al., 1997). And, as with the MTL, the strength of prefrontal activity predicted subsequent memory performance in the Brewer et al. (1998) and Wagner et

al. (1998, Experiment 2) studies. The left posterior temporal cortex has also shown increased activity for deep, relative to shallow encoding (Decety et al., 1997; Wagner et al., 1998, Experiment 1), and to predict subsequent memory performance (Wagner et al., 1998, Experiment 2). These findings suggest that semantic encoding (and thus better remembering) is associated with increased activity in the MTL, prefrontal cortex, and posterior temporal lobe.

Although these regions act in concert, human lesion and functional brain imaging data suggest that they play different roles at encoding. Semantic information needed to support object naming and word reading is stored in a network of regions that includes posterior temporal cortex (for review see Martin, 1998). The selection and retrieval of this information is dependent on left prefrontal cortex (e.g., Thompson-Schill et al., 1997). In addition, prefrontal cortex serves to organize information at the time of encoding (Moscovitch, 1992), and for left prefrontal cortex, this working memory function may be specific to semantic encoding (Gabrieli et al., 1998). The MTL is inter-connected with both of these regions and, thus, perfectly positioned to receive organized information from prefrontal cortex and to mediate information storage in the temporal lobe and other regions of the cortex (Squire, 1992; Eichenbaum et al., 1996).

Reading real words and naming real objects are associated with the automatic engagement of a number of processes. These include activating stored semantic information about the concepts to which the words and objects refer, and the processes necessary to support selection and retrieval of this information. At the same time, the experience of naming and reading, along with other event-specific contextual information must be organized for efficient storage into memory. These functions are mediated by a network of regions that includes the left MTL. Material that automatically engages semantic processing will increase left MTL activity over and above the level associated with similar types of material that do not have pre-existing semantic representation.

In contrast, the right MTL appeared to have an all or none pattern of activity with regard to processing different types of material. Objects produced a strong response in the right MTL, regardless of meaning. Words produced no detectable right MTL response, even when a liberal statistical criterion was employed (i.e.,  $P < .05$ , uncorrected). Thus, the question arises as to what characteristics or variables modulate right MTL activity?

## NOVELTY, AROUSAL, AND THE RIGHT MTL: WHEN (AND WHERE) NOTHING MINUS NOTHING EQUALS SOMETHING

In a series of papers, Tulving and colleagues argued that the MTL is part of a novelty detection network (Tulving et al., 1994, 1996). This argument was based on the finding that the MTL was significantly more active in response to new words (meaningful words that had not previously been presented during the experiment) than for old words (previously studied words). Novelty-related MTL activity has typically been lateralized to the right

# meaningful material - meaningless material

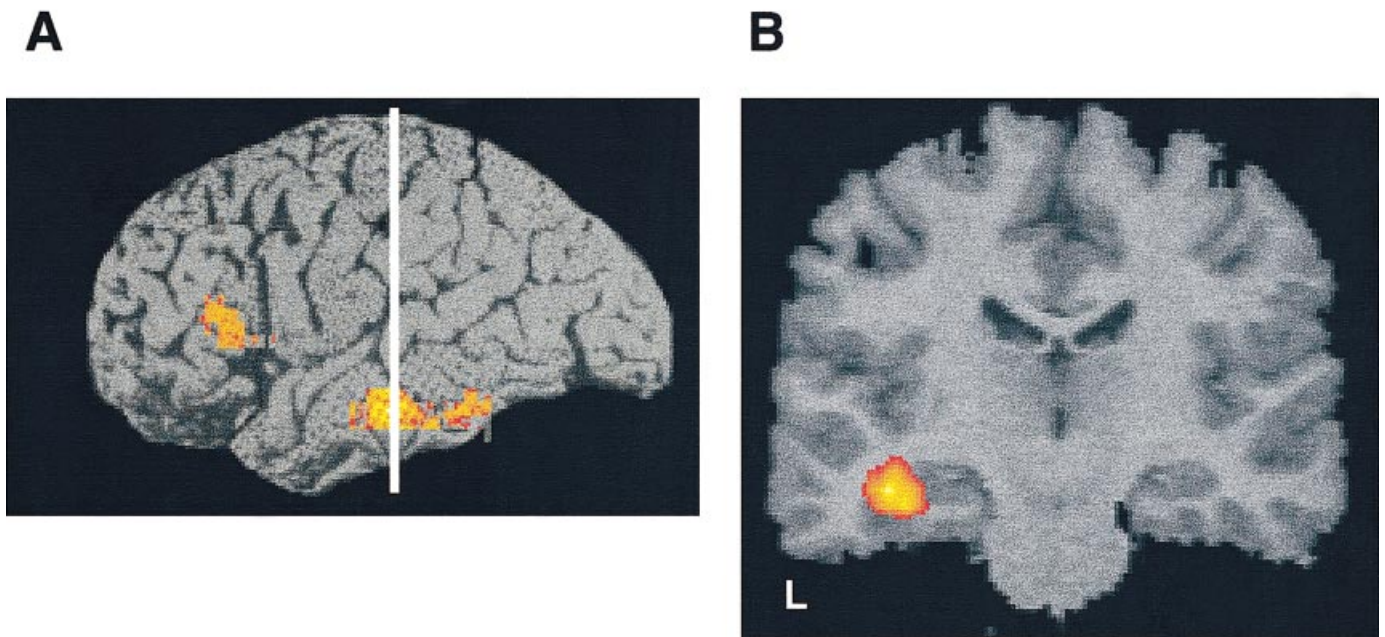


Figure 1

# visual noise - visual noise

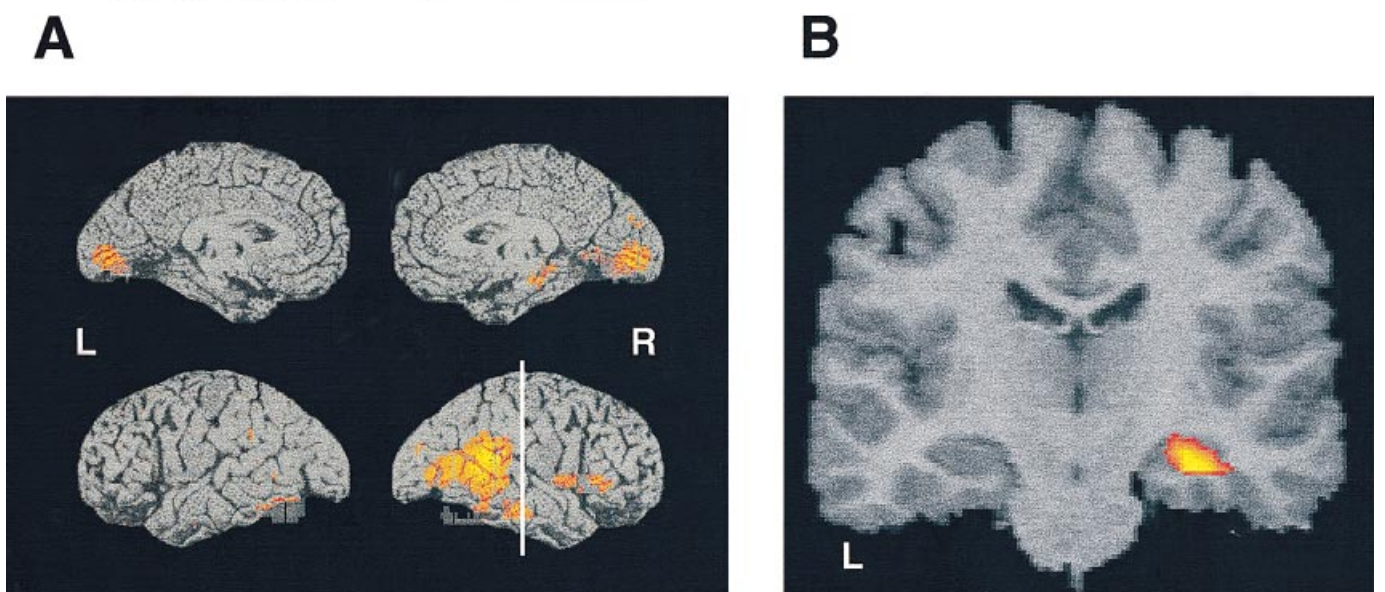


Figure 2



(Tulving et al., 1994, 1996; Nenov et al., 1994; but see Dolan and Fletcher, 1997, for greater left MTL activity for new versus old words).

As we noted previously (Martin et al., 1997), novelty can be defined in several ways. First, as in the above-cited experiments, novelty can be defined by recent experience with specific items. In a typical memory experiment, words that were not presented during the study phase are more novel than words that were presented, even though all the words are equally familiar based on life-time experience (i.e., matched for frequency of usage). The difficulty with defining novelty in this way is that it is indistinguishable from repetition priming. Functional brain imaging studies in humans, and single-cell recordings in monkeys, have demonstrated that neural activity is decreased the second time an item is processed, relative to the first time (for reviews see Schacter and Buckner, 1998; Wiggs and Martin, 1998). As a result, new words may appear to elicit greater activity relative to old words, because activity associated with processing old words has been reduced by priming. It may be argued that greater MTL activity for new vs. old words does not reflect priming because the behavioral phenomenon of priming remains normal following MTL lesions. The claim, however, is only that the MTL can show a decreased neural response with item repetition, not that this region is necessary for priming to occur. Indeed, both the human and

animal data show that decreased neural responses with item repetition can be recorded from many regions, including occipital, temporal, parietal, and prefrontal cortex, and, in the monkey, entorhinal and perirhinal cortex (for review see Wiggs and Martin, 1998).

Second, novelty can refer to meaning. Items without pre-existing semantic representations are more novel than items that have an agreed upon semantic interpretation. In this sense, nonsense objects and words are more novel than meaningful objects and words. Our study provided little support for the idea that either the left or right MTL preferentially responds to this type of novelty. The left MTL responded less to novel material (nonsense words and objects) than familiar material (real words and object), and the right MTL did not respond to nonsense words and gave the same response to objects, regardless of their meaning.

A third way novelty can be defined is with regard to general context. Tasks are more novel the first time they are performed than subsequent times. This may be especially so when the environment in which these tasks are performed is itself particularly novel. Subjects have a lifetime worth of experience reading words and viewing objects, but not while lying in the tube of an MRI scanner or with their head in a PET scanner. Within these environments, it might be reasonable to suspect that the first time a task is performed is particularly more novel than the second time.

In our study, there were two scans of each of the five conditions, presented in a pseudorandom order so that the first scan of each condition occurred before the second scan. As we reported, direct comparison of the first scans with the second scans (and, therefore, the first half of the experiment to the second half) revealed a striking pattern of predominantly right hemisphere activations, especially posterior temporoparietal cortex and the MTL. In contrast, left MTL activity remained constant with task repetition.

Although the tasks were repeated, the individual items were not. Therefore, the decreased activity could not be due to item-specific repetition priming. Rather, we suggested that this decreased activity may be related to decreased arousal or habituation during the course of the study. This habituation response, however, did not occur in all brain regions, but was confined to a specific network of areas, mostly lateralized to the right hemisphere and including the right MTL.

The decline in right, but not left, MTL activity was seen the second time each task was performed relative to the first. Inspection of the data, however, suggested that the largest decrease occurred for the visual noise conditions (see figure 4 in Martin et al., 1997). Although the word and object encoding conditions were presented in different orders during the first and second halves of the experiment, the visual noise baseline conditions were always the first and last scans (occurring approximately 100 minutes apart). Therefore, the fact that repeating this condition showed the largest decrease in MTL activity suggested the possibility of a general decline in level of arousal or habituation during the study.

A direct comparison of the two visual noise conditions is presented in Figure 2. As with the analysis that compared the first

**Fig. 1.** Location of activations that exceeded a threshold of  $Z > 3.09$ ;  $P < .001$ , for naming real objects and reading real words, relative to viewing nonsense objects and reading nonsense words. A: Lateral view of the left hemisphere. White vertical line indicates approximate location of coronal section shown in B. B: Coronal section, 24 mm posterior to the anterior commissure showing location of left MTL activity. Peak activations, expressed in millimeters as coordinates in the Talairach and Tournoux brain atlas (Talairach and Tournoux, 1988), were in the left fusiform gyrus  $-40$ ,  $-44$ ,  $20$ ;  $Z$  score =  $3.45$ , and  $-34$ ,  $-40$ ,  $-20$ ;  $Z = 3.54$ ; the left inferior temporal gyrus  $-48$ ,  $-44$ ,  $-16$ ,  $Z = 3.44$ , left MTL  $-38$ ,  $-24$ ,  $-16$ ,  $Z = 4.17$ ; and left inferior prefrontal cortex  $-44$ ,  $+24$ ,  $+8$ . Not shown are a more dorsally located left prefrontal activation ( $-44$ ,  $+10$ ,  $+28$ ,  $Z = 2.85$ ), and a left cerebellar activation ( $-24$ ,  $-56$ ,  $-28$ ,  $Z = 2.91$ ) revealed at a slightly lower statistical threshold. No activations were located in the right hemisphere.

**Fig. 2.** Location of activations that exceeded a threshold of  $Z > 3.09$ ;  $P < .001$ , for the first visual noise viewing condition relative to the second. Scans occurred approximately 100 minutes apart. A: Lateral and medial views of the left and right hemispheres. White vertical line on the right lateral view indicates approximate location of coronal section shown in B. B: Coronal section, 23 mm posterior to the anterior commissure, showing location of right MTL activity. Peaks of this activation were located at  $+26$ ,  $-26$ ,  $-12$ ,  $Z = 3.92$ ; and  $+20$ ,  $-20$ ,  $-16$ ,  $Z = 3.90$ . Additional right MTL activations were located more posteriorly at  $+20$ ,  $-30$ ,  $-4$ ,  $Z = 3.41$ ; and  $+16$ ,  $-36$ ,  $-4$ ,  $Z = 3.35$ . The left anterior temporal activation was at  $-30$ ,  $-8$ ,  $-24$ ,  $Z = 3.19$ . Extensive activations of the right hemisphere included medial occipital cortex, ventral occipitotemporal cortex, middle and superior temporal gyrus, inferior parietal gyrus, insula, and inferior prefrontal cortex. Smaller and weaker left hemisphere activations were located in medial occipital cortex, ventral occipitotemporal cortex, and middle temporal and inferior parietal gyri. Complete listing of stereotaxic coordinates is available from the author.

occurrence of all conditions to the second, the right MTL, right posterior temporoparietal and inferior frontal cortices, and the left anterior temporal lobe near the amygdala, were all more active during the first visual noise scan relative to the last. These findings, including the change in right MTL activity, were replicated by an analysis of PET data from another study in which the visual noise patterns were also presented during the first and last scans (Wiggs et al., 1999; as a result, only the last visual noise scan was used as a baseline in that study).

The locations of these activations were consistent with findings from patients with focal lesions, and suggest that specific regions of the brain, including the MTL, are involved in the maintenance of tonic arousal and attention. Damage to the right posterior temporoparietal cortex often produces neglect of left hemispace, and reduced arousal and orienting response as measured by galvanic skin response (GSR) (for review see Heilman et al., 1985). Moreover, focal unilateral damage confined to the MTL also results in a reduced orienting response (Knight, 1996). This effect may be greater after right than left MTL lesions. For example, right temporal lobectomy patients show a greater reduction of GSR and faster habituation to auditory stimuli than left temporal lobectomy patients and normal individuals (Fedio and Martin, 1983; Davidson et al., 1992). Activation of this network, including the right MTL, may signal the occurrence of novel events, situations, and environments. Activity may decline as these occurrences become more familiar, leaving the network free to respond to the next novel situation.

## SUMMARY AND CONCLUSIONS

The data presented and reviewed here suggest the following:

1. The MTL is automatically engaged whenever an event is attended to and subjects engage in the type of processing that spontaneously occurs in response to a particular type of stimulus. Reading words, identifying objects, and even staring at nonsense objects were all associated with MTL activity. Hemispheric asymmetries in MTL activation may occur as an automatic by-product of lateralized processes needed to encode different types of material (verbal, nonverbal). Similar hemispheric asymmetries in MTL activity would be expected when subjects engage in different modes of processing that may be asymmetrically represented (e.g., coordinate vs. categorical spatial analysis, part-whole decomposition vs. holistic analysis of shape).
2. Material that naturally engages semantic processes (reading real words, naming real objects) produces greater activation of the left MTL than material that does not normally engage these processes (nonsense words, nonsense objects). Greater activation of the left MTL for meaningful material relative to meaningless items may be an automatic by-product of left-lateralized semantic processing mechanisms located in prefrontal and temporal cortices.
3. The intention to learn may serve to increase the strength of encoding-related MTL activity, but is not necessary for learning nor for MTL activation. Once we attend to a word, we cannot

prevent reading. Once we attend to an object, we cannot prevent naming. And, once we encode for meaning, we are likely to remember.

4. The MTL is part of a network of regions that are differentially responsive to novelty. Increased MTL activation, especially in the right, may be associated with increased arousal and vigilance that, in turn, increase the detection of, and memory for, novel events. The decision to store new information may be dependent, at least in part, on whether this information already exists in long-term storage. As Tulving has suggested, novelty detection and assessment may be an early stage of encoding by which adaptively significant events are identified for additional processing (Tulving et al., 1996).

5. The use of a baseline comparison task similar to the visual noise stimuli may increase the likelihood of finding MTL activity in functional brain imaging studies that rely on comparing different conditions, or different single event types, to reveal activations. The effectiveness of this baseline condition may be related to its ability to capture a subject's attention without placing demands on specific cognitive processes. In contrast, other baseline conditions, such as staring at a constantly present fixation cross, or "rest" with eyes closed, may be too unconstrained to prohibit ongoing mental activity that could obscure encoding-related activations.

This last claim assumes that the mental activity that subjects spontaneously engage in during "rest" and "fixation" would include activation of the MTL. Evidence in support of this possibility has recently been obtained by Binder and colleagues (1998) using fMRI. Relative to a simple tone discrimination task, they found that having subjects rest with eyes closed was associated with activation of a network of left hemisphere regions that included prefrontal cortex, posterior temporal cortex, and the MTL. In other words, the same network that is active during semantic encoding. Binder and colleagues documented this by showing that the regions active during "rest" were also active during a semantic processing task, relative to the tone discrimination task. Thus one would expect that a "rest" baseline may be a particularly poor comparison condition for revealing activations related to semantic processing and encoding. To provide one example, as reviewed previously, Price et al. (1994) reported activation of the left MTL when subjects read words relative to performing a feature-detection task on false font stimuli. However, in another study in which words were presented for reading under the same stimulus presentation conditions, but compared to "rest with eyes closed," no MTL activations were revealed (Price et al., 1996a).

## FINAL COMMENTS

The findings reviewed here bring functional brain imaging evidence in line with other sources of data on MTL functioning during encoding. In addition to providing converging evidence, these findings serve to highlight a number of issues about

encoding-related MTL activity that it may now be possible to address with functional brain imaging. These include a better understanding of the effects that different types of novelty, and changes in attention and awareness, have on MTL activation. It will also be critical to determine whether the different components of the MTL memory system (hippocampus and surrounding cortical structures) have qualitatively distinct functions (see recent Commentaries by Mishkin et al., 1998; Squire and Zola, 1998; Tulving and Markowitsch, 1998).

If the MTL is necessary to form new declarative memories then these structures must be active whenever events are experienced. Evidence that these structures are automatically engaged as a by-product of stimulus processing is consistent with models of MTL functioning based on findings with amnesic patients (Moscovitch and Umiltà, 1990; Moscovitch, 1995) and with models based on the properties of hippocampal LTP (Morris and Frey, 1997). In addition, the findings reviewed here suggest a hemispheric division of labor that goes beyond material-specific effects. The left MTL appears to be modulated by meaning, whereas the right MTL may be particularly responsive to novelty, both of which result in better remembering.

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